UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/609,019 | 06/26/2003 | Richard K. Cooper | 51687-0101 (287015) | 8431 |

23370 7590 06/26/2006

JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
ATLANTA, GA 30309

| EXAMINER | |
|---|---|
| SINGH, ANOOP KUMAR | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | |

DATE MAILED: 06/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/609,019 | COOPER ET AL. | |
| | Examiner | Art Unit | |
| | Anoop Singh | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21 and 52-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,52-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/06/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

### *Election/Restrictions*

Applicants election on telephone and reaffirmation of the telephonic election with traverse of the invention of group I (Claims 1-21) is acknowledged.

Applicant's amendment filed on May 30, 2006, has been received and entered. Claims 22-51 have been canceled, while claims 52-72 have been added. Applicants have also amended claims 1, 2, 3, 7, 11 and 18.
Claims 1-21 and newly added claims 52-72 are under consideration in the instant application.

### *Specification*

The objection to the specification is withdrawn in view of amendments to the specification filed by Applicant's on May 30, 2006.

### *Withdrawn-Claim Rejections - 35 USC § 112- Second Paragraph*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Applicant's amendment in claims 1, 2, 3, 7, 11 and 18 are found persuasive. Therefore, claims 1-21 previously rejected under 35 USC § 112 as being vague and indefinite are withdrawn.

***Withdrawn-Claim Rejections - 35 USC § 112-First Paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicant's arguments see page 13, 14 and 16, filed on May 30, 2006, with respect to Claims 1-21 have been fully considered, and are persuasive. The rejection of claims 1-21 has been withdrawn.

***New-Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6, 8-10 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480) taken with Fischer et al (PNAS, 2001, 98 (12), 6759-6764).

Cooper taught a vector comprising a gene encoding a transposase operably linked to a promoter, Mo transposon insertion sequences recognized by the transposase; and an exogenous gene located between the transposon insertion sequences. The promoter directing expression of the transposase gene may be inducible. See the claims. In column 8, at lines 58-67 Cooper listed transposases, including Tn10 and Tn5, which may be used in combination with the same vector. The claims require a modified transposase gene, wherein one to twenty codons, preferably the first ten, at a beginning of the gene are modified by changing a nucleotide at a third base position of the codon to an adenine or thymine without changing the amino acid encoded by the codon.

Such claim limitations embrace not only mutated but also wild-type transposase genes. There is no sequence of a starting transposase gene and a resulting modified transposase gene sequence. Therefore, the claim limitations are met by any transposase gene having an A or T in the third position of codons one to twenty at a beginning, preferably the in the first ten codons, of the transposase gene. It would appear inherent that any transposase gene would comprise a codon having an A or T in the third position of codons one to twenty at a beginning, preferably the in the first ten codons. Cooper exemplified use of the Tn10 gene but did not provide its sequence. The Examiner however has provided a partial sequence of a beginning of a Tn5 transposase gene that comprises codons having an A or T in the third position in support of the inherency assertions. See for example, Schulz et al (J. Mol. Biol., 1991, 221: 65-80), which taught a Tn5 gene sequence having codons with an A or T in the third position. See figure 2 on page 69 in particular see the codons immediately upstream or downstream of the AUG codon. Cooper et al discussed use of both constitutive and inducible promoters for directing expression of both the transposase gene and the gene of interest. See for example, columns 15-18. Cooper sought to

express transgenes in various vertebrates as evidenced by the teachings in column 9, in lines 40-50. Cooper differed from the claimed invention by not teaching a promoter comprising a modified Kozak sequence that comprises ACCATG or a vector comprising more than one gene of interest operably linked to more than one promoter between the transposase insertion sequences.

However, at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan. It was also well known at the time the invention was made that an expression cassette may comprise more than one gene of interest in operable linkage with more than one promoter. For example, Meiss et al taught a vector for providing expression of a gene of interest in either prokaryotic or vertebrate cells. The vector comprised a CMV promoter in operable linkage with a Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. The vector also comprised a T7 promoter in operable linkage with bacterial ribosome binding site and Kozak sequence operably linked to a reporter gene and a sequence encoding a histidine tag. The Kozak sequence is interpreted to be part of the promoter since it is located upstream of the translation initiation site, in the 5' untranslated region. This interpretation has been made since the specification has not provided a definition of a promoter sequence. In addition, since the reporter gene and histidine tag coding sequences are different they are interpreted to read on two separate genes of interest, which are operably linked to two different promoters as taught in the vector of Meiss et al. See Figure 1, in panel B on page 476 and also throughout pages 478 and 480. Meiss further discusses use of a CMV promoter/enhancer system. However, Meiss et al do not explicitly teach using Kozak sequence with transposase.

Prior to filing of this application, Fischer taught cloning of Kozak sequence upstream of transposase gene and at 3' to the PRM1-NX promoter resulting in vector *prm1*-Tc1 (see page 6759, column 2, para and figure 2 page 6761). Fisher et al describe use of Kozak sequence to express gene in mouse cells.

Accordingly, in view of the teachings of Meiss and Fischer it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Fischer had already shown that Kozak sequence could be used upstream of transposase gene and 3' to the promoter to express protein. In addition, it was an art-recognized goal to express a gene of interest in vertebrate cells as taught by Cooper et al, and particularly since Meiss et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells and more particularly because Meiss et al created an expression vector that comprises a Kozak sequence in operable linkage with a promoter for expressing a gene of interest in a vertebrate cell (See Figure 1, in panel B on page 476 and also throughout pages 478 and 480).

One who would practiced the invention would have had reasonable expectation of success because Fischer et al had already described use of Kozak sequence to express transposase gene in eukaryotic system. Meiss et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells and it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-11, 15-20, 52-53, 57-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480), Fischer et al (PNAS, 2001, 98 (12), 6759-6764) and further in view of Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998).

The combined teachings of Cooper, Meiss and Fischer et al have been discussed above and are relied upon in same manner. However, none of the references explicitly teaches advantage of using ovalbumin or other inducible promoters.

Hackett et al teach introducing nucleic acid encoding the SB transposase gene operably linked to a promoter. It is noted that the nucleic acid sequence comprises at least a portion of an open reading frame also preferably, the nucleic acid sequence comprises at least a regulatory region of a gene selected from the group consisting of a promoter, an enhancer (column 4, lines 29-40). Hackett et al disclose variety of promoters that could be used including constitutive promoters, tissue-specific promoters, and inducible promoters (column 12, lines 35-40). It is also noted that Hackett also contemplates a particular DNA sequence could be modified to employ the codons preferred for a particular cell type. In addition, Hackett teaches protein can be produced in quantity in milk, urine, blood or eggs by using promoters known for expression in milk, urine, blood or eggs such as ovalbumin promoter (column 16, lines 38-45).

Accordingly, in view of the teachings of Meiss and Fischer it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the vector of Cooper by inserting a Kozak sequence in the promoter such that is in operable linkage with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as Fischer had already shown that Kozak sequence could be used upstream of transposase gene and 3' to the promoter to express gene of interest. In addition, it was an art-recognized goal to express a gene of interest in vertebrate cells as taught by Cooper et al, and particularly since Meiss et al specifically taught that a Kozak sequence comprising ACCATG is the optimal sequence for initiating translation in vertebrate cells (See Figure 1, in panel B on page 476 and also throughout pages 478 and 480). The skilled artisan would be further motivated to modify the vector by including ovalbumin or other tissue specific inducible promoter to direct the expression of gene of interest in eggs or milk as taught by Hackett. It is evident that skilled artisan would have further optimized the vector by including other inducible promoters such as conalbumin or vitellogenin,

because Hackett had already described that tissue specific inducible promoters could be used to direct expression of gene of interest in the egg or milk.

One who would practiced the invention would have had reasonable expectation of success because Hackett had already described that ovalbumin promoter could be used to direct expression of the SB transposase gene in milk or egg. Fischer and Meiss had already described use of Kozak sequence to express transposase gene in eukaryotic system. Thus, it would have only required routine experimentation to modify the vector to Cooper to include Kozak sequence upstream of transposase and 3' to the promoter such as ovalbumin to direct expression of the gene in egg or milk.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-20, 52-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper R. (US 5,719,055), Meiss et al (Biotechniques, 2000, 29(3): 476, 478, and 480), Fischer et al (PNAS, 2001, 98 (12), 6759-6764), Hackett et al (US Patent no. 6489458, dated 12/3/2002, filing date 9/10/1998) and further in view of Wallace, R. A, King J.L and Sanders, G.P., (Biology: The Science of Life, 1986, Scott Foresman and Company, pp 235).

The combined teachings of Cooper, Meiss, Fischer and Hackett et al have been discussed above and are relied upon in same manner. However, none of the references explicitly teaches using two-stop codon with Poly A.

Prior to filing of this application, Wallace et al teach three stop codons UAA, UAG and UGA that are used as stop codon. It is noted that Wallace et al also disclose double stop codon such as UAA-UAG to ensure message to ribosome (pp 235, col. 2, see section polypeptide chain termination).

Accordingly, it would have been obvious and within the scope of skill for an artisan to subject the vector taught by Cooper, Meiss, Fischer and Hackett to include two-stop codon operably linked to the transposase as taught by Wallace. One of ordinary skill in the art would have been motivated to include two-stop codon to ensure

proper termination of transposase synthesis and would have also included poly A as a obvious modification for expression in mammalian system. It is emphasized that a conalbumin Poly A broadly encompasses Poly A or any signal and does not require entire non-coding region of a conalbumin for instant rejection.

One who would practiced the invention would have had reasonable expectation of success because Wallace had already described use of two stop codon to ensure polypeptide chain termination. It would have only required routine experimentation to modify the vector to include two stop codons operably linked to the gene to enhance the termination of transposase synthesis.

Therefore, the claimed invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

***Response to Arguments***

Applicant's arguments with respect to claims 1-6, 8-10 and 15-17 have been considered but are moot in view of the new ground(s) of rejection. Applicants assert that claimed invention is not rendered prima facie obvious by cited references. Applicant argue that vector of present invention allows improved expression of transposase protein, thereby resulting in a significant increase in insertion frequency (page 18, para 5). In addition, applicants argue that of cited references neither teach nor suggest a vector that uses a Kozak sequence to allow for a prokaryotic gene to be expressed and function in a eukaryotic cell *in vivo*. Applicants further assert that Meiss is concerned with a vector that may be used *in vitro*.

In response to applicant's argument it is emphasized that that the features upon which applicant relies (i.e., eukaryotic or prokaryotic transposase, insertion frequency, *in vitro* or *in vivo* expression) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, applicants argue that Meiss teaches using both prokaryotic and a eukaryotic translation initiation sequence upstream of a eukaryotic gene of interest to allow for expression of eukaryotic gene in either prokaryotic or eukaryotic cells. Applicants argue that Meiss does not describe or suggest use of a Kozak sequence for expression of a transposase protein (pp 19, para 1). Further it is also argued that Cooper teaches that a transposase based vector comprising a gene that may be designed without the Kozak sequence, thus Cooper does not provide motivation to include a Kozak sequence as means to improve vector.

In response, contrary to the applicants argument, cited reference of Miess taught a vector for providing expression of a gene of interest in either prokaryotic or vertebrate cells (supra, pp 476, col. 3, para 2; pp 480, col. 1, para 2). It is apparent that a skilled artisan would be motivated to modify the vector disclosed by Cooper to include Kozak sequence as disclosed by Meiss (pp 478, col. 2, para 1) to express a gene of interest in vertebrate cells. It is emphasized that at the time the claimed invention was made inclusion of a Kozak sequence in an expression vector for optimal translation initiation of a gene in vertebrate cells was within the routine skill level of the ordinary artisan as disclosed by Meiss et al. Although, it is noted that cited publication does not teach Kozak sequence for the expression of transposase protein that may be prokaryotic or eukaryotic as argued by the applicants (pp 19, para 1 of the argument). However, cited art teaches use of Kozak sequence in expressing prokaryotic or eukaryotic gene (supra). Furthermore, it is art recognized that translation initiation of prokaryotic protein in eukaryotic stem is generally poor and Kozak sequences are widely used to enhance the expression of prokaryotic protein in eukaryotic cells. For example, prior to the instant application, Fischer et al (PNAS, 2001, 98, 12, 759-6764) also show the use of Kozak sequence upstream of transposase gene and at 3' to the PTN promoter-suggesting use of Kozak sequence to express protein in mouse cells. It is noted that in absence of any specific promoter requirement in rejected claims, it would be *prima facie* obvious to one skilled in the art to modify the vector of Cooper to include Kozak sequence upstream of transposase gene as it would have further optimized the expression of prokaryotic protein in eukaryotic cell as suggested by Meiss.

***Conclusion***

Claims 1-20 and 52-72 are not allowed.

The following art made of record and not relied upon is considered pertinent to applicant's disclosure:

Koga et al (J Human Genet, 2003, 48: 231-235, published online 3/28/2003) teach pHe103 plasmid (figure 1) tyrosinase gene, Tol2 transposase and translation start and stop codon in helper plasmid pHe103. It is noted that nucleic acid sequence 3' to the CMV promoter comprises the Kozak sequence (ACCATG), the Kozak sequence being positioned to include the first codon of the Tol2 transposase. Koga et al is not applied as prior art due to earlier priority date of instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272- 0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph.D.
AU 1632

Joel Weitzman
AU 1632